

## 64 SECTION 1 / Cancer Biology

In carcinomas such as colon and lung cancer, the initiation of neoplasia has been shown to involve oncogene and tumor suppressor gene mutations.<sup>151</sup> These mutations are generally thought to result from chemical carcinogenesis, especially in the case of tobacco-related lung cancer, where a novel tumor suppressor gene (designated FHIT) has been found to be inactivated in the majority of cancers, particularly in those from smokers.<sup>152,153</sup> In preneoplastic adenomas of the colon, the *K-ras* gene is often mutated.<sup>154</sup> Progression of colon adenomas to invasive carcinoma frequently involves inactivation or loss of the *DCC* and *p53* tumor suppressor genes. Gene amplification is often seen in the progression of some carcinomas and other types of tumors. Amplification of the *erb B-2* oncogene may be a late event in the progression of breast cancer.<sup>100</sup> Members of the *myc* oncogene family are frequently amplified in small cell carcinoma of the lung.<sup>99</sup> As mentioned previously, amplification of *N-myc* strongly correlates with the progression and clinical stage of neuroblastoma.<sup>98</sup> Although there is variability in the pathways of human tumor initiation and progression, studies of various types of malignancy have clearly confirmed the multistep nature of human cancer.

## SUMMARY AND CONCLUSIONS

The initiation and progression of human neoplasia is a multistep process involving the accumulation of genetic changes in somatic cells. These genetic changes then consist in the activation of cooperating oncogenes and the inactivation of tumor suppressor genes, which both appear necessary for a complete neoplastic phenotype. Oncogenes are altered versions of normal cellular genes called proto-oncogenes. Proto-oncogenes are a diverse group of genes involved in the regulation of cell growth. The functions of proto-oncogenes include growth factors, growth factor receptors, signal transducers, transcription factors, and regulators of programmed cell death. Proto-oncogenes may be activated by mutation, chromosomal re-arrangement, or gene amplification. Chromosomal re-arrangements that include translocations and inversions can activate proto-oncogenes by deregulation of their transcription (e.g., transcriptional activation) or by gene fusion. Tumor suppressor genes, which also participate in the regulation of normal cell growth, are usually inactivated by point mutations or truncation of their protein sequence coupled with the loss of the normal allele.

The discovery of oncogenes represented a breakthrough for our understanding of the molecular and genetic basis of cancer. Oncogenes have also provided important knowledge concerning the regulation of normal cell proliferation, differentiation, and programmed cell death. The identification of oncogene abnormalities has provided tools for the molecular diagnosis and monitoring of cancer. Most important, oncogenes represent potential targets for new types of cancer therapies. It is more than a hope that a new generation of chemotherapeutic agents directed at specific oncogene targets will be developed. The goal of these new drugs will be to kill cancer cells selectively while sparing normal cells. One promising approach entails using specific oncogene targets to trigger programmed cell death. One example of the accomplishment of such a goal is represented by the inhibition of the tumor-specific tyrosine kinase *bcr/abl* in CML.<sup>155</sup> Our rapidly expanding knowledge of the molecular mechanisms of cancer holds great promise for the development of better combined methods of cancer therapy in the near future.

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